UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/899,569	07/06/2001	Norbert Schweifer	0652.2280001/EKS/AES	1574

26111 7590 02/26/2004

STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/899,569	SCHWEIFER ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *1,5 and 7-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-4 and 6* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *02/17/04* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group II, claims 2-4, 6, in Paper No.12 of 10/24/02 is acknowledged and entered.

Claims 1-9 are pending in the instant application and Claims 1, 5, 7-9 have been withdrawn from further consideration by the Examiner under 37 CFR 1.142(b) as being drawn to non-elected invention.

Group II, Claims 2-4, 6 are currently under prosecution.

The traverse is as follows:

The claims of groups I-III should be examined together, because the search for one group is likely to uncover art of interest to the other groups, and thus it would not be a serious burden for the Examiner to examine all the groups.

The traverse is not found to be persuasive for the following reasons:

The DNA molecule of group II is structurally different from the polypeptide of group I and the antibody of group III. Therefore, the searches for the three groups are not co-extensive, and it would be a serious burden for the Examiner to search and examine all the groups together.

The requirement is still deemed to be proper and therefore made FINAL.

Accordingly, group II, claims 2-4, 6 are examined in the instant application.

PRIORITY DATE

The Examiner has established a priority date (07/06/2001) for the instantly claimed application serial number 09/899569 for the following reasons:

1) The application 60/243158 to which priority is claimed does not recite SEQ ID NO:3 or 4. The recited SEQ ID NO:1 in the application 60/243158 seems to be different from SEQ ID NO:3 of the instant application, and

2) The other applications 60/297,747, filed on 06/14/2001, DE 100 33 080.0, filed on 10/25/2000 and DE 101 19 294.0, filed on 06/14/2001 do not have a translated copy, and therefore their written description cannot be fully assessed. Applicant is invited to submit an English translation of said applications.

MPEP 119, item b-3 teaches that the Director may require a certified copy of the original foreign application, specification, and drawings upon which it is based, a translation if not in the English language, and such other information as the Director considers necessary. Any such certification shall be made by the foreign intellectual property authority in which the foreign application was filed and show the date of the application and of the filing of the specification and other papers.

Applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

OBJECTION

1. Claim 2 is objected to because claim 2 depends on non-elected claim 1. Further, claim 2 appears to be free of prior art but is objected to as being dependent upon a non-elected claim, but would be allowable if rewritten in independent forms, including all of the limitations of the base claim.

2. Claim 3 is objected to because it is not clear "fragment thereof" is a fragment of the DNA molecule according to claim 2, or a fragment of the hybridizing polynucleotide, or a fragment of SEQ ID NO:3.

3. The specification is objected to because part of page 1a is empty space.

INFORMATION DISCLOSURE STATEMENT

The Information disclosure statement submitted on 01/11/02 cannot be found in the application.

A telephonic conversation with the Anne Summerfield requesting to resubmit the information disclosure statement was done on 02/17/04. However the information disclosure statement still has not been received by the Office.

The Information disclosure statement submitted on 01/11/02 will be reviewed when it is available.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 3-4, 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

ClaimS 3-4, 6 are indefinite because claim 3 is drawn to "stringent hybridization conditions". Stringent conditions are not defined by the claim (which reads on the full range of stringent conditions, that is from very permissive to very high stringency. The specification describes a single non-limiting example of stringent conditions (p.11, second paragraph). Thus the specification does not provide a standard for ascertaining

the requisite degree of stringent conditions and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention and would not be able to determine the metes and bounds of the claims.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 3-4, 6 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 3-4, 6 are drawn to a fragment of a DNA molecule coding for **a fragment of the tumor associated antigen of SEQ ID NO:4**, characterized in that it is or contains a polynucleotide which hybridizes under stringent conditions with the polynucleotide of SEQ ID NO:3.

It is noted that an unrelated polynucleotide could hybridize with the polynucleotide of SEQ ID NO:3, via a common fragment, even under the most stringent hybridization conditions.

Further, stringent conditions encompasses from very low to very high stringency, wherein under very low stringency unrelated sequences would hybridize to the polynucleotide of SEQ ID NO:3.

The findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that [a] written description of an invention involving a chemical genus, like a description of a chemical species, "requires a precise definition, such as by structure, formula, [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials. Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as vertebrate insulin cDNA or mammalian insulin cDNA without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of the hybridizing polynucleotide, per Lilly by structurally describing a representative number of the hybridizing polynucleotides, or by describing structural features common to the

members of the genus, which features constitute a substantial portion of the genus. Alternatively, per Enzo, the specification can show that the claimed invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

In this case, the specification does not describe the hybridizing polynucleotide required to practice claims 3-4, 6 in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any hybridizing polynucleotide, other than the polynucleotide of SEQ ID NO:3, nor does the specification provide any partial structure of such hybridizing polynucleotide, nor any physical or chemical characteristics of the hybridizing polynucleotide, other than the polynucleotide of SEQ ID NO:3, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single polynucleotide, SEQ ID NO:3, this does not provide a description of the hybridizing polynucleotides that would satisfy the standard set out in Enzo.

The specification also fails to describe the hybridizing polynucleotides by the test set out in Lilly. The specification describes only a single polynucleotide, SEQ ID NO:3. Therefore, it necessarily fails to describe a representative number of such species. In addition, the specification also does not describe structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Thus, the specification does not provide an adequate written description of the hybridizing polynucleotides that is required to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. Claims 3-4, 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotide of SEQ ID NO:3, or polynucleotides encoding SEQ ID NO:4, **does not reasonably provide enablement for a polynucleotide which hybridizes under stringent conditions with the polynucleotide of** SEQ ID NO:3 or a fragment thereof, or a pharmaceutical composition containing said polynucleotide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 3-4, 6 are drawn to a DNA molecule coding for **a fragment of the tumor associated antigen of SEQ ID NO:4**, characterized in that it is or contains a polynucleotide which hybridizes under stringent conditions with the polynucleotide of SEQ ID NO:3.

It is noted that an unrelated polynucleotide could hybridize with the polynucleotide of SEQ ID NO:3, via a common fragment, even under the most stringent hybridization conditions.

Further, stringent conditions encompasses from very low to very high stringency. However, neither the specification nor the claims define what is meant by stringent conditions. The definition of stringent conditions on page 11, second paragraph in the specification, is non-limiting, due to the language "for example". As conventionally understood in the art and as taught by US Patent No. 5,912,143, hybridization is used to

refer to any process by which a strand of nucleic acid binds with a complementary strand through base pairing (col 5, lines 3-5) and further teaches that numerous equivalent conditions may be employed to comprise either low or high stringency conditions and hybridization solutions my be varied to generate conditions of either low or high stringency (col 5, lines 57-67). The "stringent hybridizing" as claimed read on both high and low stringency conditions. It is well known that the lower the stringency condition the more dissimilar the hybridizing molecule will be from the molecule to which it hybridizes. For example, Sambrook et al, eds, 1989, 2nd ed, Molecular Cloning, a laboratory manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, p. 11.52, teach that the temperature of hybridization, (which is related to the degree of stringency) should be high enough to suppress hybridization of the probe to incorrect sequences. Sambrook et al further teach that if the probe hybridizes indiscriminately, repeat the hybridization at a higher temperature or wash under conditions of higher stringency (p. 11.52, last two lines).

Thus claims encompass polynucleotides comprising non-disclosed nucleic acid sequences which are attached to a non-specific fragment of SEQ ID NO:3.

When given the broadest reasonable interpretation, the claims are clearly intended to encompass a variety of species including full-length cDNAs, genes and protein coding regions. Clearly, it would be expected that a substantial number of the hybridizing molecules encompassed by the claims **would not** share either structural or functional properties with SEQ ID NO:3.

The specification however does not disclose how to make such hybridizing molecules.

In view of the above, one of skill in the art would be forced into undue experimentation in order to use the claimed invention as broadly as claimed.

2. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising the polynucleotide of SEQ ID NO:3, or polynucleotides encoding SEQ ID NO:4, **does not reasonably provide enablement for "pharmaceutical composition for cancer immunotherapy"**, containing as active ingredient SEQ ID NO:3, or polynucleotides encoding SEQ ID NO:4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 6 is drawn to "pharmaceutical composition for cancer immunotherapy", containing as active ingredient:

a) a DNA molecule coding for the tumor associated antigen designated B345, characterized in that it has the amino acid sequence defined in SEQ ID NO:4 or contains this as part of its sequence, or a fragment thereof, or

b) a recombinant DNA molecule coding for the tumor associated antigen of SEQ ID NO:4, characterized in that it is a polynucleotide of SEQ ID NO:3, or contains this sequence, or it is or contains a polynucleotide which hybridizes under stringent conditions with SEQ ID NO:3 or a fragment thereof.

Inherent in a pharmaceutical composition is in vivo use thereof.

The specification discloses that SEQ ID NO:3 is overexpressed in bowel cancer or colon adenocarcinoma as compared to normal control tissue, as shown by quantitative PCR (p.33, 43-46).

The specification discloses that the B345 DNA molecules may be used in a "so-called" DNA vaccine for the immunotherapy of tumors (p. 11, last paragraph).

There is however no disclosure concerning data from using SEQ ID NO:3 for immunotherapy of cancers.

Claim 6 reads on a DNA molecule of SEQ ID NO:3 or fragments thereof, for use in gene therapy for immunotherapy of cancer (p.12, lines 1-7).

On cannot extrapolate the teaching in the specification to the scope of the claim. The state of the gene therapy art at the time of filing was that the combination of vector, promoter, protein, cell, target tissue, level of expression and route of administration required to target the tissue of interest and obtain a therapeutic effect using gene therapy was unpredictable. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period

of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

Further, it is well known in the art that cancer immunotherapy is unpredictable. The specification however provides no exemplification of or guidance on how to use the claimed pharmceutical formulation for active immunotherapy in humans. The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to

eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1).

Furthermore, Boon (Adv Can Res, 1992, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). In addition, Boon teaches even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph).

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or

use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the unpredictability of gene therapy and immunotherapy, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, YVONNE EYLER can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS
PATENT EXAMINER
February 19, 2004